"The Feasibility of a Cochlear Nucleus Auditory prosthesis based on microstimulation"

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SUMMARY AND ABSTRACT

The overall goal of this contract is to develop an auditory prosthesis based on multisite microstimulation within the cochlear nucleus. One objective is to develop arrays of microelectrodes that can be implanted with minimal injury to the nervous tissue. During the last quarter we have continued our evaluation, in the cat model, of the tissue injury caused by implanting arrays of long (4.5 mm) closely-spaced (400 μm) discrete, activated iridium microelectrodes. The length and spacing of the electrodes are comparable to those that can be implanted into the human cochlea nucleus with the aid of a tool inserted through the translabyrinthine surgical approach to the CP angle. We compared the incidence of significant interstitial hemorrhages (infarcts) after implanting electrodes with sharp conical tips (approximately 3 μm in diameter at the tip) and blunt conical tips (tip diameter approximately 15 μm). To date, the tracks of 9 of the 18 blunt electrodes has been examined histologically (3 weeks to 5 months after implantation) and none show any histologic evidence of new or healed infarcts. Nine other electrodes remain in vivo, and based on the very low thresholds of the evoked responses, we conclude that there are no infarcts of significant size near their tips. This is a much more favorable outcome than was obtained with the arrays of long, closely-spaced sharp electrodes, in which 6 of 18 electrodes produced interstitial hemorrhages and subsequent infarcts.

We have developed an alternative method of generating the response growth functions (recruitment curves) of the evoked potentials induced in the cochlear nucleus and recorded in the inferior colliculus. The curves are generated during the actual high-rate stimulation regimen, while pulsing at 250 to 500 Hz. These "imbedded" recruitment characteristics have revealed some short-term depression of synaptic transmission in the lower auditory pathway that is not apparent in the recruitment curves generated shortly after the end of the prolonged stimulation. Although the short-term effects are not really a safety issue, they are relevant to the performance of an auditory prosthesis based on intranuclear microstimulation, and in this context, they suggest that the stimulus pulse rate during prolonged stimulation regimens should not

exceed 250 Hz to each microelectrode.

We pulsed 2 electrodes in one cat (cn108) for 7 hours per days on each of 15 successive days. The regimen was conducted 5 months after implantation of the arrays of blunt-tipped microelectrodes. The stimulus was a 250 Hz pulse train, modulated over the range of 6 to 20 μA, according to the logarithmically-compressed artificial voice signal (described previously). The duty cycle of the artificial voice was 50% (15 sec on, 15 sec off, at 6 μA). There was little or no cumulative effect on neuronal excitability beyond the second day of stimulation, and the neural tissue and neurons surrounding the electrodes sites appeared to be completely normal, and indistinguishable from the tissue surrounding the unpulsed site.

METHODS

Fabrication of stimulating microelectrodes.

Activated iridium stimulating microelectrodes were fabricated from lengths of pure iridium wire 50 μm in diameter. A Teflon-insulated lead wire was welded to one end of the iridium shaft, and the other end was shaped to a conical taper, by electrolytic etching. The entire shaft and wire junction was then coated with 3 thin layers of Epoxylite 6001-50 heat-cured electrode varnish. The insulation was removed from the tip by dielectric destruction. The individual electrodes were then assembled into an integrated array of 2 to 4 microelectrodes spaced 400 μm apart. The integrated array, with its closely-spaced microelectrode shafts, was designed to approximate the dimensions of an array that can be implanted into the human posteroventral cochlear nucleus using a tool inserted through the translabyrinthine surgical approach to the CP angle. The shafts of the electrodes extend 4 mm beyond the array's superstructure. Electrodes of this 4 to 5 mm in length will be required to reach all the way through the human ventral cochlear nucleus.

The iridium electrodes are then "activated" to increase their charge capacities, soaked in deionized water for 120 hours, and sterilized with ethylene oxide.

Implantation of stimulating and recording electrodes

Young adult cats were anesthetized with Pentothal, with transition to a mixture of nitrous oxide and Halothane. Implantation of the electrodes was conducted using aseptic surgical technique. The cat's head was placed in a stereotaxic frame, and the skull was exposed as far back as the posterior fossa by reflecting the scalp and muscles. A pair of stainless steel recording electrodes, with their exposed tips (approximately 0.4 mm in length), and separated vertically by approximately 8 mm, was inserted by stereotaxis into the right inferior colliculus through a small craniectomy. The deeper electrode was positioned just below the central nucleus of the colliculus, and the upper electrode was placed dorsal to the surface of the colliculus. The compound action potential induced by a train of clicks delivered to the left ear was used to position the recording electrodes. The introducers surrounding the electrodes were then retracted and the shafts of the electrodes were cemented to the skull by flooding the small craniectomy with methylmethacrylate.

A small craniectomy was made in the posterior fossa over the cerebellum, through which the integrated array of 2 or 3 iridium stimulating electrodes was inserted by stereotaxis into the left posteroventral cochlear nucleus (pvcn). Since the feline cochlear nucleus lies on the lateral surface of the brainstem and the human cochlear nucleus is buried behind the middle cerebellar peduncle, the feline array of 4 mm microelectrodes was inserted through a portion of the overlying cerebellar flocculus, so that we could evaluate electrodes whose length was appropriate for use in humans. The microelectrodes were positioned first by stereotaxic coordinates and the final positioning was achieved by observing the potential evoked in the inferior colliculus while stimulating with the microelectrode.

Stimulation protocols and data acquisition

At intervals after implantation, the recruitment curves of the evoked responses were recorded in the inferior colliculus. Stimulation and data acquisition was conducted using the two-way radiotelemetry stimulation and data acquisition system described

previously (QPR # 4, Contract NO1-NS-2-2323). This telemetry system and its companion software allows continuous monitoring of the voltage waveform across the stimulating microelectrodes, and of the compound evoked potential induced in the inferior colliculus by the stimulating microelectrodes. The responses evoked by 1024 to 4096 consecutive charge-balanced, controlled-current stimulus pulses applied to the stimulating microelectrodes were averaged to obtain an averaged evoked compound action potential (AECAP). For each AECAP, the amplitude of the first or second component was measured after the averaged response is filtered through a low-pass filter with a bandwidth of 250 to 2.5 kHz. The amplitude of the early and second components is measured from the peak of the positivity on the leading edge to the trough of the subsequent negativity. The response growth function (recruitment curve), which representing the recruitment of the excitable neural elements surrounding the microelectrode, is generated by plotting the amplitude of the first or second component of each of several AECAPs against the amplitude of the stimulus pulse .

The "conventional" recruitment curves were generated before and immediately after the sessions of prolonged stimulation. The stimulus frequency was 50 Hz. The novel "imbedded" recruitment curves were acquired during the session of prolonged stimulation at 250 to 500 Hz, using newly developed custom computer software. Additional details of this technique are presented later in this report.

RESULTS

The relation between the microelectrode's tip configuration and the incidence of interstitial hemorrhage (infarcts).

One of our objectives is to minimize the amount of tissue injury during insertion and residence of discrete iridium microelectrodes and arrays of thin-film photolithographic electrodes. Our experience with implanting these probes into the ventral cochlear nucleus and cerebral cortex has shown that the primary source of tissue injury is the large interstitial hemorrhages that occur during, or within a few days after, implantation of the probes. These large hemorrhages occurs when the probes

sever the interstitial blood vessels. We have fabricated discrete iridium microelectrodes with conical shanks that terminate in either an angled ellipsoidal facet or in a spherical tip with various radii of curvature. The range of tip configurations is illustrated in Figure 1. The electrodes are insulated with Epoxylite heat-cured varnish which is removed from the tip either by mechanical abrasion (facets) or by dielectric destruction (spherical tips). In the cochlear nucleus, microelectrodes with faceted tips inflict a relatively low incidence of interstitial hematoma, although there have been several occurrences of hematomas with these. However, the faceted tips are very difficult to produce when the electrode shafts are long (4-5 mm) as will be required for implantation into the human cochlear nucleus.

We compared the incidence of interstitial infarct from long microelectrodes with sharp (3 μm-diameter) and blunt (15 μm-diameter) spherical tips. Nine arrays containing 35 sharp electrodes with 4 mm shafts, were inserted into the posteroventral cochlear nuclei of 8 cats. One implant failed when the percutaneous connector dislodged from the skull. Of the remaining 8 arrays, 3 failed completely within a week after implantation, due to interstitial infarct. In these animals, the threshold of the evoked response recorded in the inferior colliculus became very high (greater than 15 μA) and the animals were sacrificed for histologic evaluations. In each case this revealed a large hemorrhagic infarct in the cochlear (QPR#3). In addition, there were smaller infarcts around 3 other sharp microelectrodes. This frequency of significant interstitial infarcts is unacceptable for a device intended for human use, and we therefore have been evaluating microelectrodes with blunter tips in the hope that, during implantation, they would displace rather than sever the interstitial blood vessels. Eighteen blunt microelectrodes (tip diameters 15 μm) in 6 arrays of 3 electrodes have now been implanted. The threshold of the evoked response from all 18 microelectrodes has remained below 8 μA for at least 3 weeks after implantation, indicating no interstitial hemorrhages or scars large enough to interfere with their functioning.. Nine of the electrode sites have been evaluated histologically, 3 weeks to 5 months after implantation. Two cats were sacrificed 3-4 weeks after implantation

when the blunt microelectrodes actually began to push through the ventral surface of the cochlear nucleus. This produced an elevation in the threshold of the evoked response, and the animals were then sacrificed. This unusual failure mode, which had not been observed previously, is probably due to the tendency for arrays of blunt microelectrodes to displace tissue, and also the fact that the feline cochlear nucleus is a pendulous structure on the lateral aspect of the brainstem, and is easily displaced by the pressure from the array during implantation. When the displaced tissue slowly returns to its original shape, the array, whose matrix is partly buried in the overlying cerebellum, may be driven downwards through the tissue. The result is illustrated in Figure 2, from cat CN109. The histologic section shows part of the track of 2 of the 3 microelectrodes and part of the surrounding glial sheath (scale bar=250 μm). There is an aggregation of mononuclear cells and lymphocytes near the tip of one microelectrode, where it had begun to protrude through the pia on the ventral surface of the cochlear nucleus. Numerous macrophages surround a patent area which appears to have been the site of a microelectrode's tip. However, there is no evidence of new or healed interstitial infarcts adjacent to any part of the electrode tracks or elsewhere in the cochlear nucleus. Virtually all of the nearby neurons appear normal, with only an occasional perineuronal halo. The results were similar for cat CN110, in which the implant failed in a similar manner. Although the loss of these animals from the long-term series is unfortunate, it did provide an opportunity to examine the tracks of the blunt microelectrodes at a relatively early stage after implantation. One additional cat implanted with blunt microelectrodes was used in a 15-day stimulation experiment, 5 months after implantation. The histology from this animal (CN108) is described below. In this case also, there was no evidence of healed interstitial hemorrhages. Nine electrodes remain implanted in 3 cats, and the threshold of their evoked responses remains below 8 μA, indicating that there are viable neurons within 30 μm of the tips. We have fabricated 3 additional arrays of blunt microelectrodes, and we will implant these within the next 2 months. However, the results to date with the blunt microelectrodes are very encouraging. The tissue displacement problem noted in cat

CN109 and CN110 is not likely to be a factor in human implants, since the human cochlear nucleus is completely buried in the posterior pons, rather than a pendulous structure on the lateral surface of the brainstem, like the feline nucleus.

Measurement of the response growth function generated during simulated acoustic stimulation.

We have made extensive use of the response growth function (recruitment curve) of the compound response that is evoked by the microelectrodes in the ventral cochlear nucleus and recorded in the central nucleus of the inferior colliculus. The "conventional" recruitment curves are acquired at a stimulus pulse rate of 50 Hz, to give sufficient time between pulses (20 msec) to capture the entire evoked response. When measured before and at various times after several hours of high-rate stimulation the "conventional" recruitment curves reveal any persisting stimulation-induced depression of neuronal excitability. While such persisting effects are relevant to the question of the safety of the stimulation regimen, the curves so acquired do not reveal short-acting refractory or inhibitory effects that may be relevant to the performance of an implant based on intranuclear microstimulation. To address the latter, we developed a computerized data acquisition scheme in which the acquisition of the recruitment curves is embedded in the high-rate artificial voice signal.

We have simulated an acoustic environment by using a computer-generated artificial voice The artificial voice reproduces many of the characteristics of real speech, including the long-term average spectrum, the short-term spectrum, the instantaneous amplitude distribution, the voiced and unvoiced structure of speech, and the syllabic envelope. The artificial voice signal is then passed through a full wave rectifier and then undergoes logarithmic amplitude compression, before being sent through an appropriate anti-aliasing filter. The amplitude of the signal from the filter then sets the amplitude of the charge-balanced stimulus pulses which are delivered to each electrode at 250 or 500 Hz, in an interleaved manner. The range of spike amplitudes is shifted upwards so that acoustic silence is represented by a stimulus amplitude of 6 μA,

which is close to the response threshold of the neurons near the tip of the properly functioning microelectrodes.

Figure 3 illustrates the process of acquiring the imbedded recruitment curves. The logarithmically compressed, full-wave rectified artificial voice signal from the anti-aliasing filter is used to set the amplitude of the stimulus pulses. The embedded recruitment curves are generated for each of several stimulus pulse amplitudes (e.g., 6, 8, 10, 12, 20, 24 μA), one amplitude level at a time. When the appropriate pulse amplitude (e.g., 6 μA) is generated by the artificial voice, subsequent stimulus pulses are suspended for 8 msec, which is long enough for the first and second components of the evoked response to be recorded in the inferior colliculus. Pulsing at the full stimulus rate or 250 or 500 Hz then resumes, and the computer waits 100 msec before resuming its search for the next 6 μA pulse, at which time another evoked response is recorded. This is repeated until the required number of responses to 6 μA is collected and averaged. Typically, 1,024 to 4,096 responses are averaged to generated an averaged evoked response (AECAP), depending upon the signal-to-noise ratio. The entire process is then repeated for a pulse amplitude of 8 μA, 10 μA, etc., until the complete recruitment curve from that microelectrode is generated. More than 90 minutes is required to generated the embedded recruitment curve for each microelectrode vs. approximately 5 minutes when the curve is generated in the conventional manner. Therefore, it is not practical to routinely generate the embedded curves, particularly when several microelectrodes are being pulsed. However, the embedded curves do provide data that is relevant to the design of the long-term stimulation studies, as discussed below.

Figure 4 shows the AECAP recorded from the inferior colliculus in cat CN112. In this case, both the early and second components of the AECAP were large, and this expedited the process of acquiring the embedded response. Figure 5 shows recruitment curves from the early (directly evoked) component of the AECAP. The conventional recruitment curve (solid line) was acquired with a stimulus pulse rate of 50 Hz, when no artificial voice signal was present. The other curves were acquired from

stimulus pulses embedded in the artificial voice signal, as described above. The pulse rate was 250 or 500 Hz to each microelectrode. When the pulse rate was 250 Hz, the conventional and embedded recruitment curves are quite similar, and both predict the same response threshold and approximately the same growth of the evoked response with stimulus amplitude. When the amplitude-modulated pulse train was delivered at 500 Hz, the threshold of the embedded recruitment curve also is identical to that of the conventionally-acquired recruitment curve, but its slope is significantly less. Figure 5 shows that the conventionally-acquired recruitment curves do accurately predict the essential features of the direct response of neurons in the cochlear nucleus during high rate stimulation. However, the situation is somewhat different when we consider the second component of the AECAP, which represents neuronal activity evoked transsynaptically by the microstimulation in the cochlear nucleus. The conventionally-acquired recruitment curve of the second component (solid line) has the same threshold as the early component shown in Figure 5. However, the embedded recruitment curves are shifted to the right of the conventionally-acquired curve, indicating a diminution of the transsynaptically-evoked neural activity in response to low amplitude stimulus pulses. This illustrates that when we take into account transmission across synapses in the lower auditory system, there are significant short-acting refractory and/or inhibitory effects. Analogous psychophysical phenomena, usually described as "forward masking", occur in the intact auditory system. However, it is disconcerting that the short-term effects of the electrical stimulation on synaptic efficacy are much more pronounced when the stimulus pulse rate is 500 Hz. At this frequency, the imbedded recruitment curve bears little resemblance to the conventional curve. We have, therefore, decided to use a pulse rate of 250 Hz per electrode, in our long-term stimulation protocols. Recent psychophysical studies by Shannon et al (1995) indicate that when spectral information is conveyed to the proper "place" in the tonotopic gradient of the lower auditory system, the signal applied at each place requires a passband of only about 50 Hz for good intelligibility of human speech. In this context, a stimulus pulse rate of 250 Hz should be adequate to convey temporal

information sufficient for good intelligibility of human speech, if the microelectrodes are inserted into the proper place in the tonotopic organization of the ventral cochlear nucleus.

15-day stimulation protocol (CN108).

The stimulation regimen described here was part of our program to investigate the histologic and physiologic effects of prolonged microstimulation in the ventral cochlear nucleus. An array of 3 iridium microelectrodes with blunt tips (15 μm in diameter, and exposed geometric surface areas of approximately 1,000 μm^2) was implanted into the posteroventral cochlear nucleus 5 months prior to the stimulation regimen, in which two of the 3 microelectrodes were pulsed for 7 hours per day on 15 successive days. The stimulus was 250 Hz biphasic current pulses, 150 μsec/phase in duration and modulated over the range of 6-20 μA according the logarithmically-compressed artificial voice. The artificial voice signal was delivered with a 50% duty cycle; that is, 16 seconds of the artificial voice following by 16 seconds in which the stimulus amplitude was held at 6 μA. This was repeated throughout the 7-hours of stimulation. This protocol is intended to simulate a moderately noisy acoustic environment in which the sounds are primarily human speech.

Figures 7A and 7B show the recruitment curves of the early component of the AECAPS evoked by the pulsed microelectrodes (electrodes # 2 and 4) and recorded in the contralateral inferior colliculus. The recruitment curves were recorded in the conventional manner, both before and within 15 minutes after the end of each 7 hours of stimulation. During the first 2 days of the stimulation regimen, the curves became shifted slightly to the right, indicating some persisting depression of electrical excitability of the neurons very close to the microelectrodes. However, between the third and 15th session, there was little or no additional shift in the threshold of the response, and the slope of the curves did not change. This indicates that the 15-day regimen did not produce any persisting change in the electrical excitability of most of the neurons in the cochlear nucleus, and only neurons very close to the

microelectrodes were affected at all. The latter effect is revealed in the small increase in the threshold of the response between the beginning of the first day of stimulation and the end of the second day.

Immediately after the 15th day of stimulation, the cat was sacrificed for histologic evaluation of the electrode sites. The cat was deeply anesthetized with pentobarbital and perfused through the aorta with ½ strength Karnovsky's fixative (2.5% glutaraldehyde, 2% paraformaldehyde and 0.1M sodium cacodylate buffer). The cochlear nucleus and adjacent portion of the brainstem were resected, embedded in paraffin, sectioned serially in the frontal plane (approximately parallel to the shafts of the stimulating microelectrodes) at a thickness of 8 μm, and stained with Cresol Violet (Nissl stain) or with hematoxylin and eosin.

Figure 8A shows the site of the tip (T) of pulsed electrode #2 in the PVCN (Nissl stain, scale bar = 50 μm). The track is surrounded by a glial sheath 20-30 μm in thickness. There is no evidence of hemorrhage or inflammation, and the nearby tissue, including neurons and their processes, appears to be normal.

Figure 8B shows the site of the tip (T) of the other pulsed microelectrode (#4). The glial connective tissue sheath around the track is approximately 25 μm thick. There is no evidence of hemorrhage or inflammation and all of the nearby tissue appears to be normal. Figure 8C shows the site of the tip of the unpulsed (U) microelectrode (#3). The surrounding glial connective tissue sheath is 25-30 μm in thickness, approximately the same as that surrounding the pulsed microelectrodes. A portion of the sheath surrounding the shank above the tip of one of the pulsed electrodes (PT), is seen in the same section . All nearby tissue appears normal.

Figure 9 is a section through the PVCN at low magnification, and shows the tracks of 2 microelectrodes (scale bar = 250 μm). There are no areas of hemorrhage or large scars anywhere on the nucleus that might represent healed infarcts.

These physiologic and histologic findings suggest that there is no cumulative effects from 15 days of stimulation with a simulated acoustic signal (the artificial voice with a 50% duty cycle). The glial sheaths around the pulsed and unpulsed electrodes

are of the same thickness, a finding predicted by the stability of the threshold of the recruitment curves between the 2nd and 15th day. It is also notable that these microelectrodes were implanted 5 months prior to the stimulation regimen. The good condition of the tissue surrounding the shafts of the pulsed and unpulsed electrodes indicates that properly cured Epoxylite varnish may indeed be acceptable as an insulation for chronically-implanted microelectrodes. Our earlier problems with this material may have been due to the use of a suboptimal heat curing cycle.

REFERENCES

Shannon, R.V.; Zeng, F.G.; Kamath, V.; Wagonski, J. and Ekelid, M.(1995) Speech recognition with primary temporal cues. Science 270:303-304

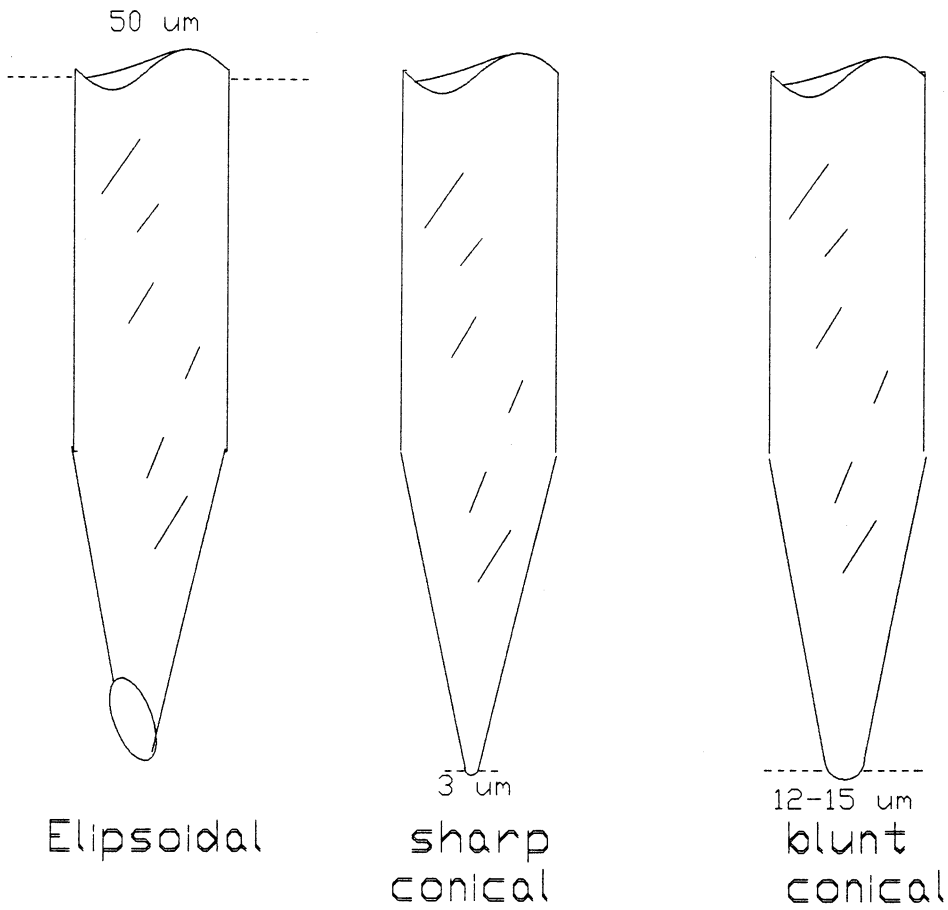

50 um
3 um
12-15 um
Elipsoidal
sharp
conical
blunt
conical
tips.skd

Figure 1

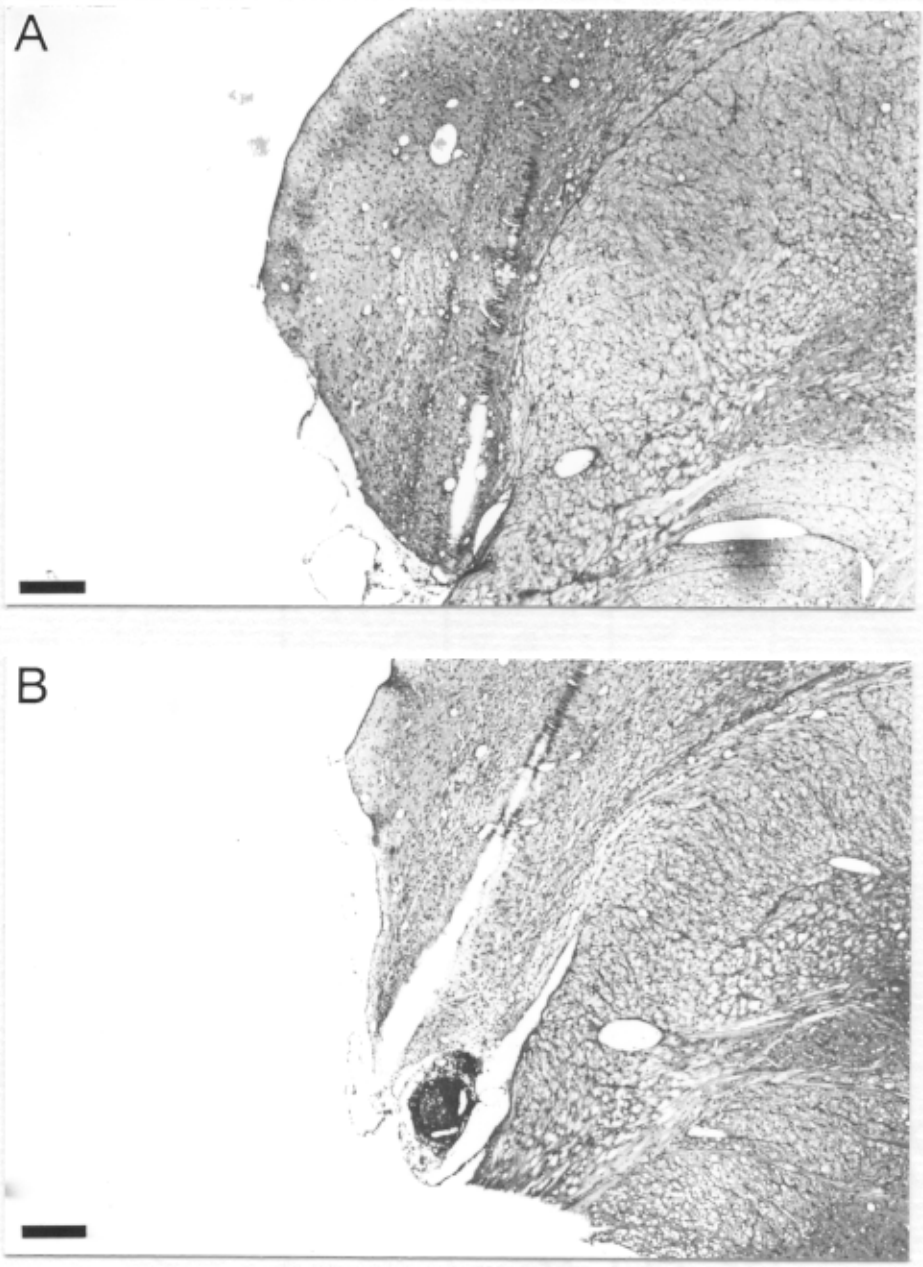


Figure 2

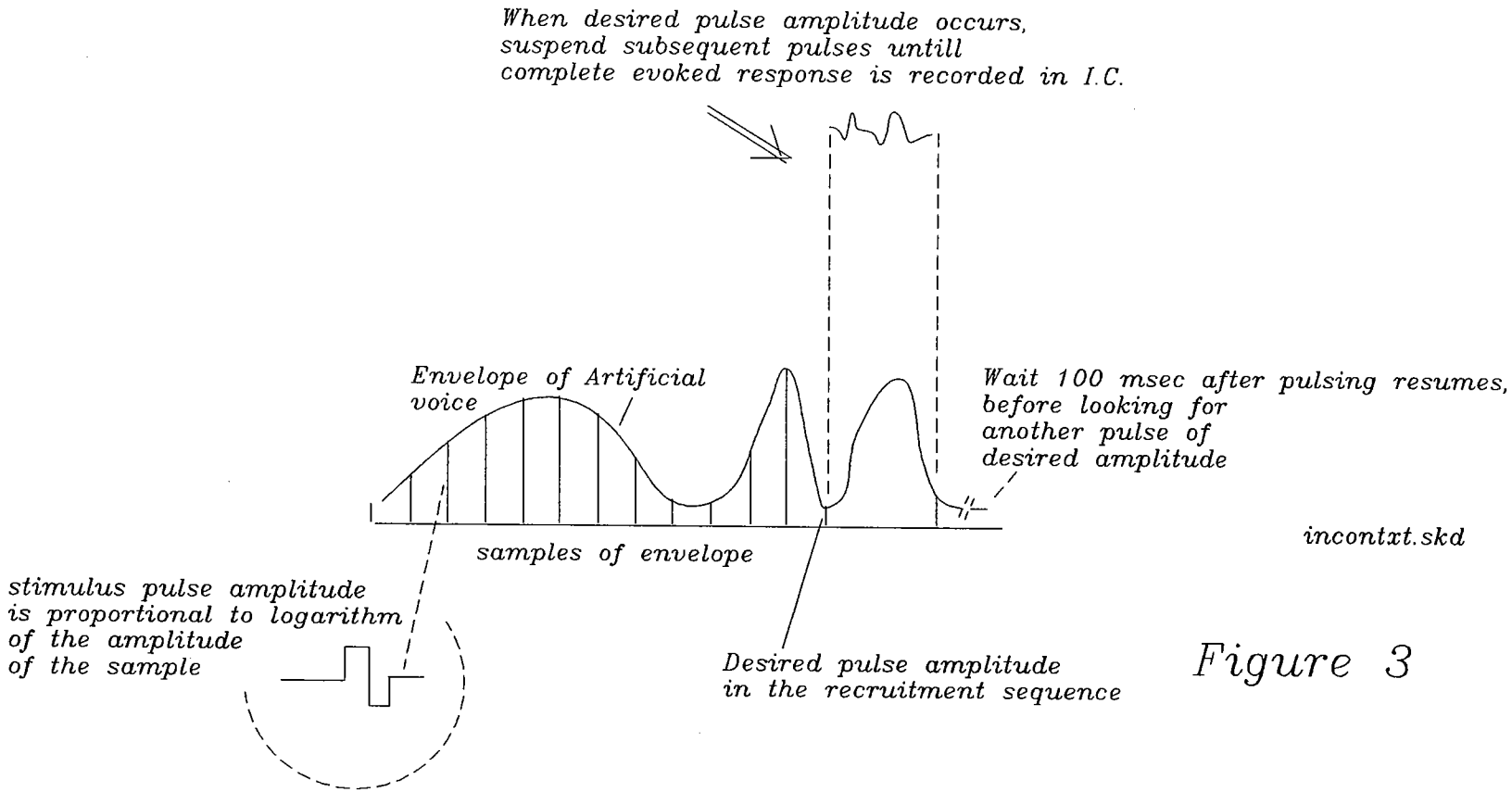
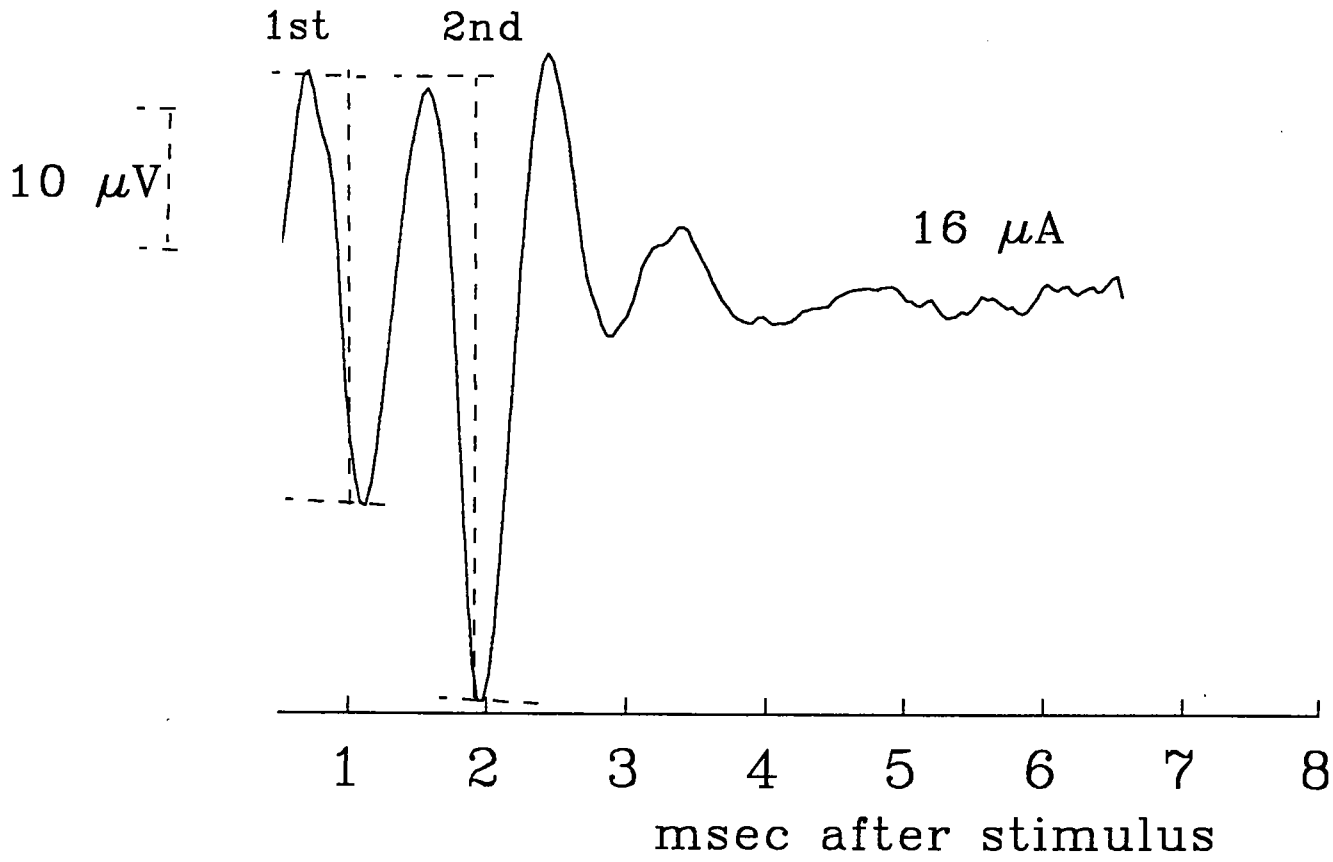

When desired pulse amplitude occurs,
suspend subsequent pulses untill
complete evoked response is recorded in I.C.
Envelope of Artificial
voice
Wait 100 msec after pulsing resumes,
before looking for
another pulse of
desired amplitude
incontxt.skd
samples of envelope
stimulus pulse amplitude
is proportional to logarithm
of the amplitude
of the sample
Desired pulse amplitude
in the recruitment sequence

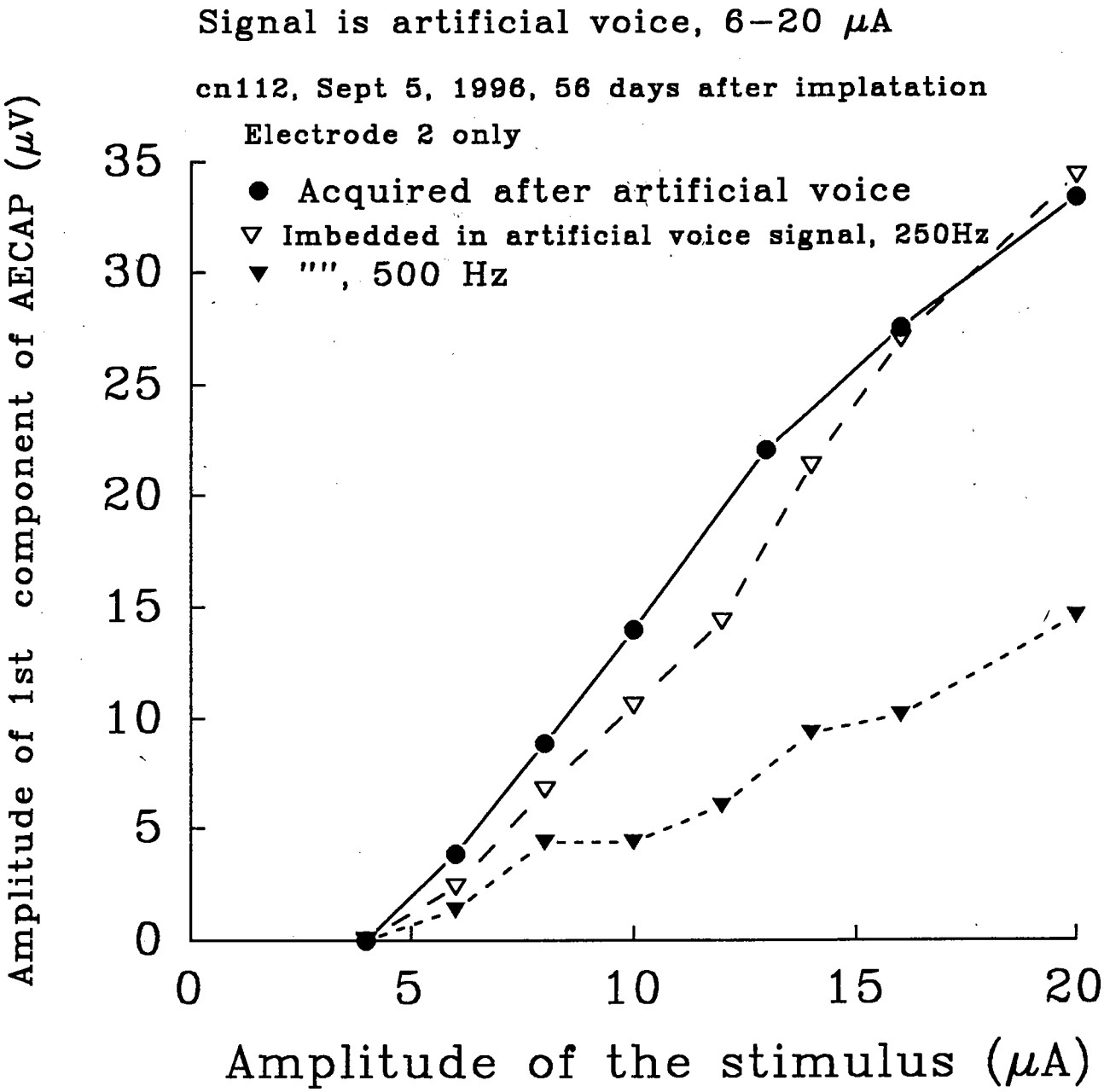
Figure 3

cn112, electrode #2 (Sept 5, 1996)
Stimulate in PVCN, record in inferior colliculus



plot41\cn\cn112tr1.spg

Figure 4



cnq112c.spg

Figure 5

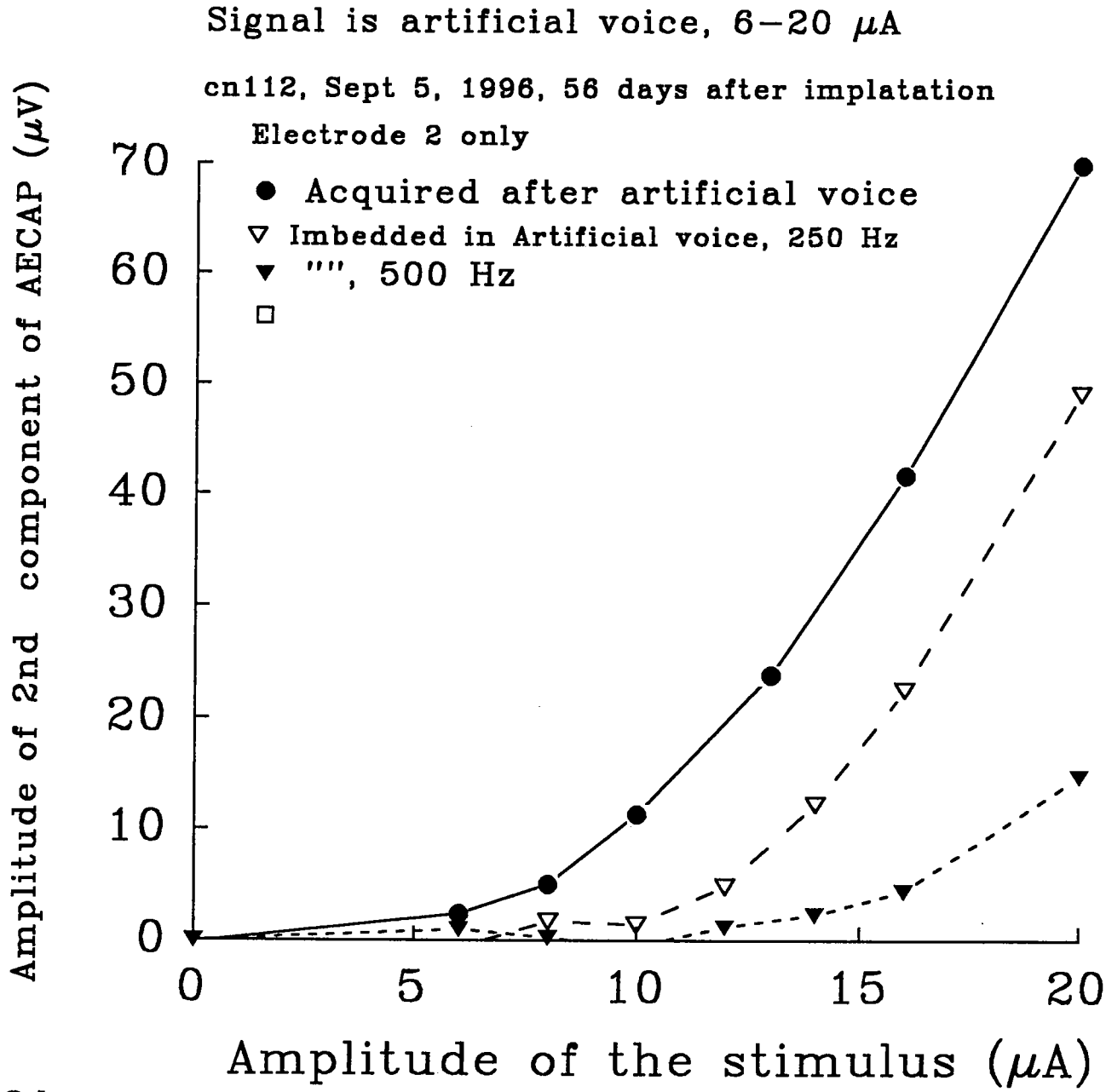


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Figure 6

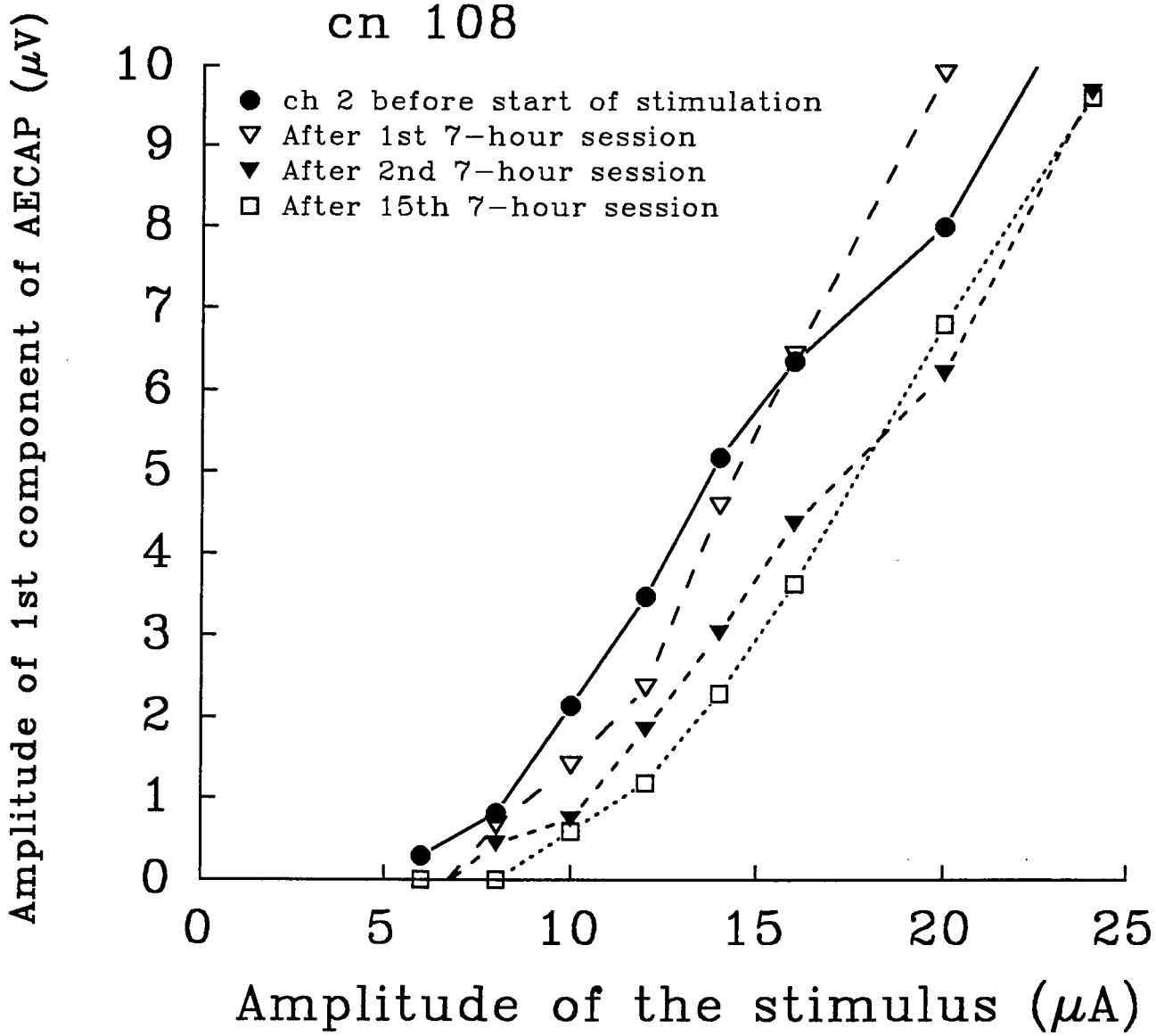

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Figure 7A

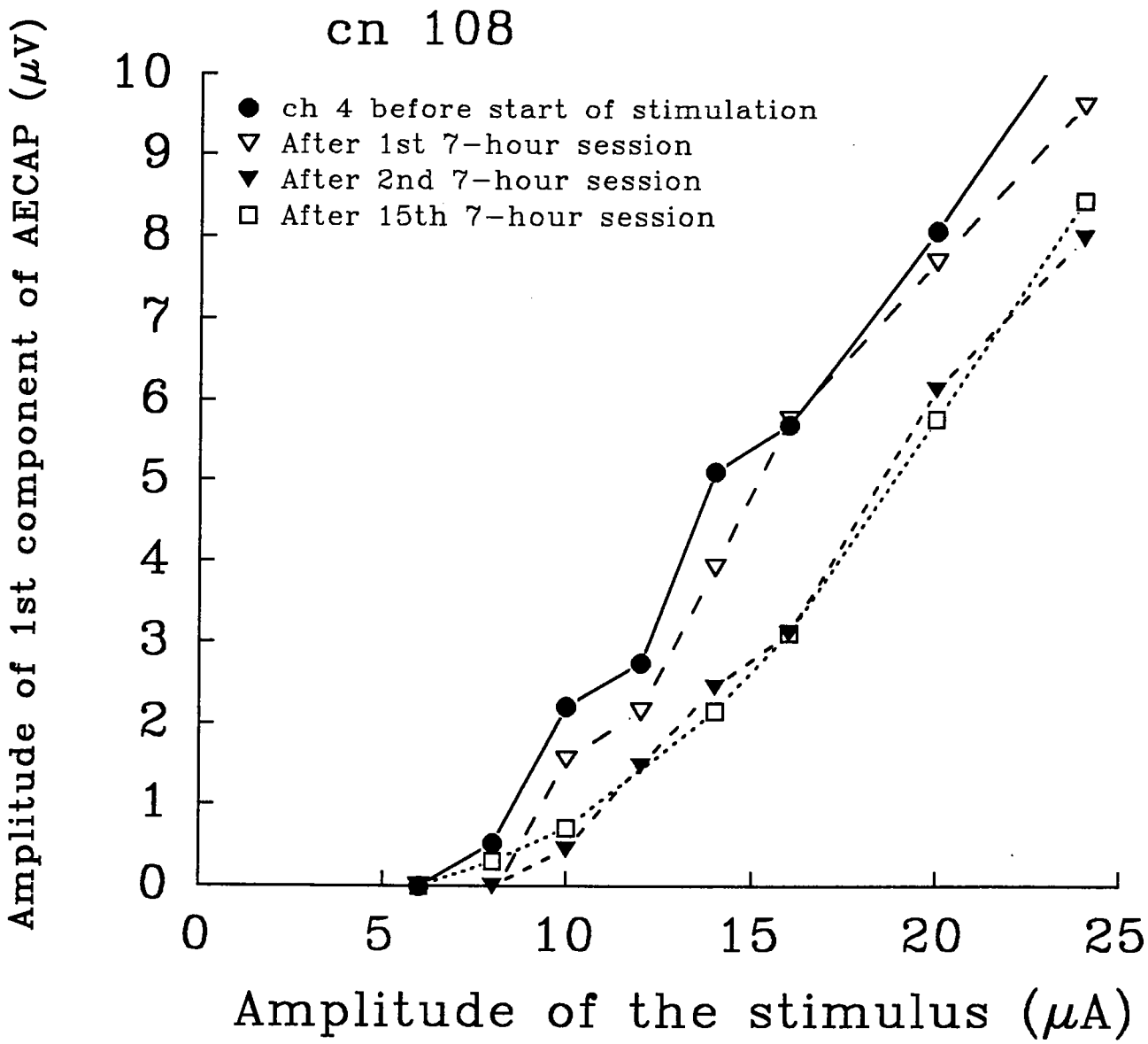

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Figure 7B

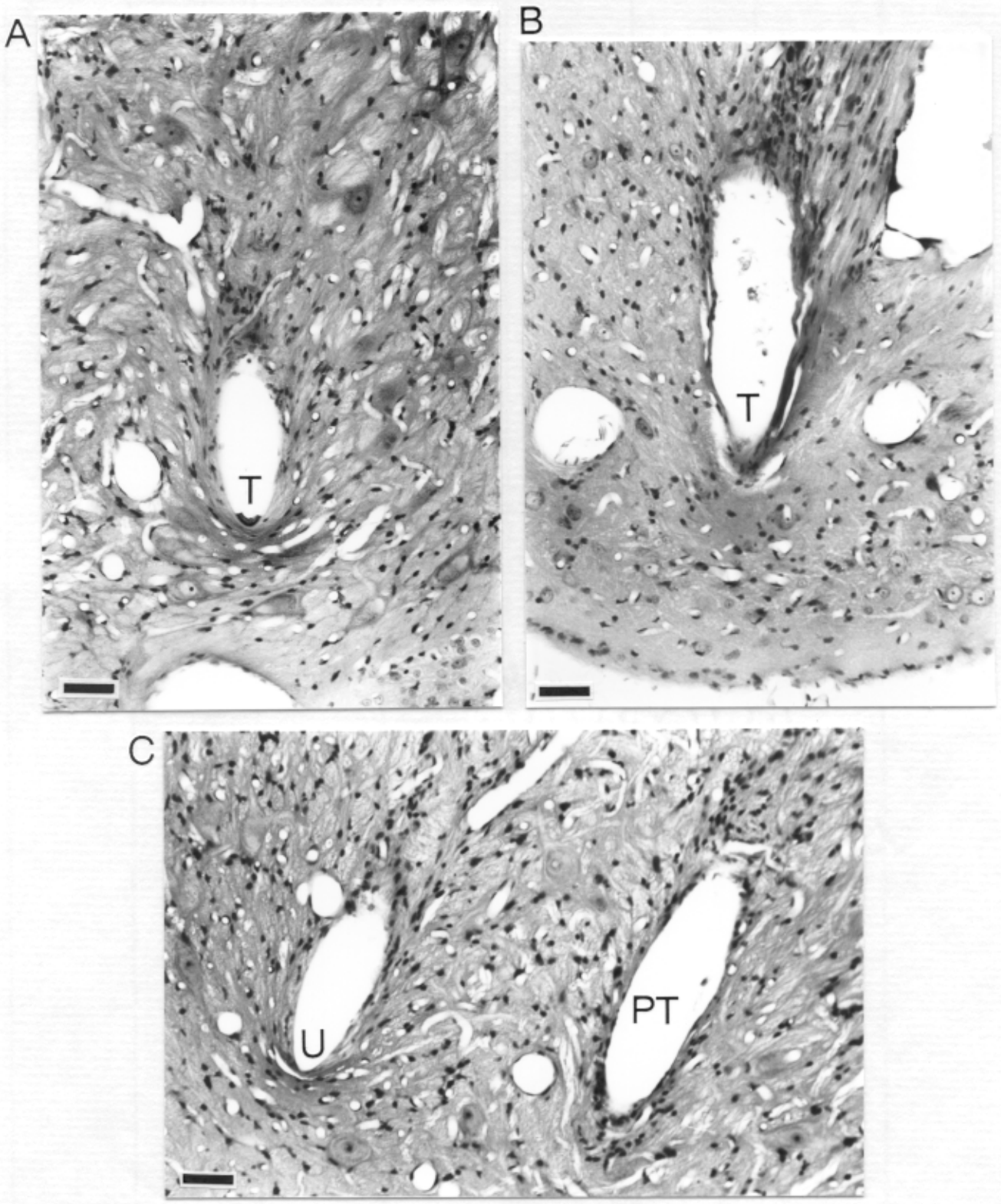

Figure 8

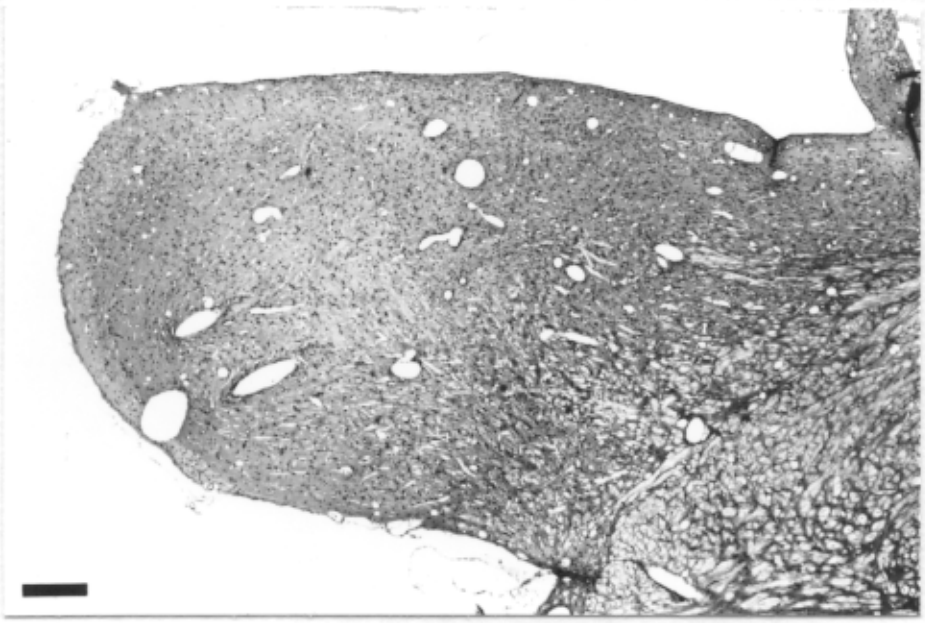

Figure 9